Docket No.: 381092000623

App No.: Not Yet Assigned Docket No.: 3810920006
Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL BLOCKERS COMPRISING TWO
BENZHYDRIL MOIETIES

Com- pound	Name	Structure
P1	3,3-Diphenyl-1-{4-[phenyl-(4- trifluoromethyl-phenyl)-methyl]- piperazin-1-yl}-propan-1-one	F F F N N
P2	3,3-Diphenyl-1-{4-[phenyl-(3-trifluoromethyl-phenyl)-methyl]-piperazin-1-yl}-propan-1-one	F F N
Р3	1-{4-[(4-Methoxy-phenyl)-(4- trifluoromethyl-phenyl)-methyl]- piperazin-1-yl}-3,3-diphenyl- propan-1-one	M e O N N N N N N N N N N N N N N N N N N
P4	1-{4-[(3,5-Di-tert-butyl-4-hydroxy-phenyl)-phenyl-methyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	HO NO STATE OF THE PARTY OF THE
P5	4-Benzhydryl-1-(3,3-diphenyl- propionyl)-piperazine-2-carboxylic acid ethyl ester	N N CO <sub>2</sub> Et
P6	1-{4-[(4-Chloro-phenyl)-phenyl- methyl]-piperazin-1-yl}-3,3- diphenyl-propan-1-one	CI

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*		
Com- pound	Name	Structure
P7	1-[4-(Benzo[1,3]dioxol-5-yl-phenyl-methyl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
Р8	4-Benzhydryl-1-(3,3-diphenyl- propionyl)-piperazine-2-carboxylic acid	H-CI N-N-O CO <sub>2</sub> H
Р9	1-{4-[(3,5-Dichloro-phenyl)- phenyl-methyl]-piperazin-1-yl}- 3,3-diphenyl-propan-1-one	CI
P10	1-{4-[(3,5-Bis-trifluoromethyl-phenyl)-phenyl-methyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	F F F O N N N N N N N N N N N N N N N N
P11	1-{4-[(4-tert-Butyl-phenyl)-phenyl-methyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	
P12	1-{4-[(2-Difluoromethoxy-phenyl)-phenyl-methyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	F F O

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Com- pound	Name	Structure
P13	1-{4-[(2,6-Dichloro-phenyl)- phenyl-methyl]-piperazin-1-yl}- 3,3-diphenyl-propan-1-one	CI H-CI
P14	1-{4-[(3,5-Dimethoxy-phenyl)- phenyl-methyl]-piperazin-1-yl}- 3,3-diphenyl-propan-1-one	MeO————————————————————————————————————
P15	1-{4-[(2,3-Dichloro-phenyl)- phenyl-methyl]-piperazin-1-yl}- 3,3-diphenyl-propan-1-one	CI O O
P16	3,3-Diphenyl-1-[4-(9H-xanthen-9-yl)-piperazin-1-yl]-propan-1-one	
P17	1-{4-[(4-Benzyloxy-phenyl)- phenyl-methyl]-piperazin-1-yl}- 3,3-diphenyl-propan-1-one	
P18	1-{4-[(2,4-Dimethyl-phenyl)- phenyl-methyl]-piperazin-1-yl}- 3,3-diphenyl-propan-1-one	

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**BENZHYDRIL MOIETIES** 

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Com- pound	Name	Structure
P19	1-{4-[Bis-(4-methoxy-phenyl)- methyl]-piperazin-1-yl}-3,3- diphenyl-propan-1-one	MeO O O O O O O O O O O O O O O O O O O
P20	1-{4-[(4-Methoxy-phenyl)-phenyl-methyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	MeO
P21	1-{4-[(4-Hydroxy-3,5-dimethoxy-phenyl)-phenyl-methyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	HO OMe MeO N N
P22	3,3-Diphenyl-1-{4-[phenyl-(2-trifluoromethyl-phenyl)-methyl]-piperazin-1-yl}-propan-1-one	F F N
P23	3,3-Diphenyl-1-[4-(phenyl-p-tolyl-methyl)-piperazin-1-yl]-propan-1-one	CH <sub>3</sub>
P24	1-{4-[(4-Fluoro-phenyl)-phenyl- methyl]-piperazin-1-yl}-3,3- diphenyl-propan-1-one	F N N N N N N N N N N N N N N N N N N N

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**BENZHYDRIL MOIETIES** 

Com- pound	Name	Structure
P25	3,3-Diphenyl-1-{4-[phenyl-(3,4,5-trimethoxy-phenyl)-methyl]-piperazin-1-yl}-propan-1-one	MeO OMe
P26	1-{4-[Benzo[1,3]dioxol-5-yl-(4-methoxy-phenyl)-methyl]-piperazin-1-yl}-3,3-diphenyl-propan-1-one	Me O N N N N N N N N N N N N N N N N N N
P27	1-[4-(10,10-Dioxo-9,10-dihydro- 10lambda*6*-thioxanthen-9-yl)- piperazin-1-yl]-3,3-diphenyl- propan-1-one	H-CI N-V
P28	3,3-Diphenyl-1-[4-(9H- thioxanthen-9-yl)-piperazin-1-yl]- propan-1-one	
P29	1-{4-[(2,4-Dichloro-phenyl)- phenyl-methyl]-piperazin-1-yl}- 3,3-diphenyl-propan-1-one	CI
P30	1-{4-[(3,4-Dichloro-phenyl)- phenyl-methyl]-piperazin-1-yl}- 3,3-diphenyl-propan-1-one	CI CI CI

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Com- pound	Name	Structure
P31	1-[4-(9H-Fluoren-9-yl)-piperazin- 1-yl]-3,3-diphenyl-propan-1-one	
P32	1-[4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P33	1-(4-Benzhydryl-piperazin-1-yl)-2- (9H-fluoren-9-yl)-ethanone	
P34	1-Bezhydryl-4-(3,3-diphenyl- propionyl)-piperazin-2-one	
P35	1-{4-[(2-Chloro-phenyl)-phenyl- methyl]-piperazi n-1-yl}-3,3- diphenyl-propan-1-one	CI
P36	1-{4-[(3-Chloro-phenyl)-phenyl- methyl]-piperazin-1-yl}-3,3- diphenyl-propan-1-one	CI ON

# Figure 1

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BENZHYDRIL MOIETIES

Com- pound	Name	Structure
P37	1-(4-Benzhydryl-2-methyl- piperazin-1-yl)-3,3-diphenyl- propan-1-one	
P38	4-Benzhydryl-1-(2-9H-fluoren-9- yl-acetyl)-piperazine-2-carboxylic acid	CO2H
P39	4-Benzhydryl-1-(2-9H-fluoren-9- yl-acetyl)-piperazine-2-carboxylic acid ethyl ester	COZE
P40	4-Benzhydryl-1-(3,3-diphenyl- propionyl)-piperazine-2-carboxylic acid	N OCCEPT
P41	4-Benzhydryl-1-(3,3-diphenyl- propionyl)-piperazine-2-carboxylic acid ethyl ester	N OCCEPTED OCCEPTED OCCUPATION OC
P42	4-Benzhydryl-1-(3,3-diphenyl- propionyl)-piperazine-2-carboxylic acid	N COSH
P43	4-Benzhydryl-1-(3,3-diphenyl- propionyl)-piperazine-2-carboxylic acid ethyl ester	COOREI

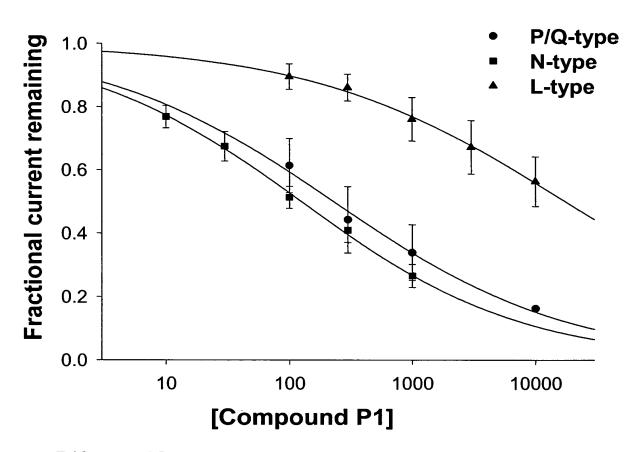
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**BENZHYDRIL MOIETIES** 

Com- pound	Name	Structure
P44	4-Benzhydryl-1-(3,3-diphenyl- propionyl)-piperazine-2-carboxylic acid amide	N N N N N N N N N N N N N N N N N N N
P45	4-Benzhydryl-1-(3,3-diphenyl- propionyl)-piperazine-2- carbonitrile	
P46	1-[4-Benzhydryl-2-(1H-tetrazol-5-yl)-piperazin-1-yl]-3,3-diphenyl-propan-1-one	
P47	1-{4-[(4-Chloro-phenyl)-phenyl- methyl]-piperazin-1-yl}-3,3- diphenyl-propan-1-one	
P48	1-{4-[(4-Chloro-phenyl)-phenyl- methyl]-piperazin-1-yl}-3,3- diphenyl-propan-1-one	
P49	1-{4-[(4-Hydroxy-phenyl)-phenyl- methyl]-piperazin-1-yl}-3,3- diphenyl-propan-1-one	
P50	1-{4-[(2,3-Dichloro-phenyl)- phenyl-methyl]-piperazin-1-yl}-2- diphenylamino-ethanone	

## Selectivity of Compound P1 for N-type Ca2+ Channels



P/Q-type IC<sub>50</sub> = 966  $\pm$  461 nM (n=7) N-type IC<sub>50</sub> = 190  $\pm$  70 nM (n=10) L-type IC<sub>50</sub> >> 10  $\mu$ M (estimated: 19.6  $\pm$  9.2  $\mu$ M) (n=5)

Figure 2

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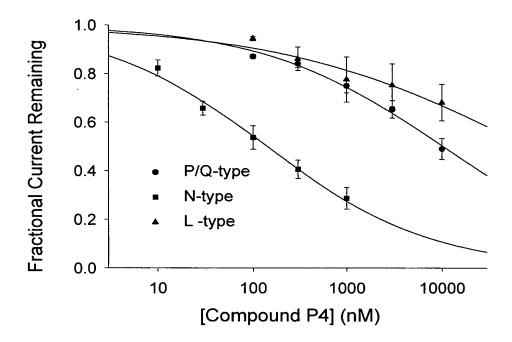
Inventor: Terrance P. SNUTCH et al.

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**BENZHYDRIL MOIETIES** 

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# Effect of Compound P4 on Various Ca2+ Channels



$$IC_{50}$$
 P/Q-type = 7592 ± 1076 nM (n=4)

$$IC_{50}$$
 N-type = 185 ± 68 nM (n=5)

$$IC_{50}$$
 L-type >> 10  $\mu$ M (n=5)

Figure 3

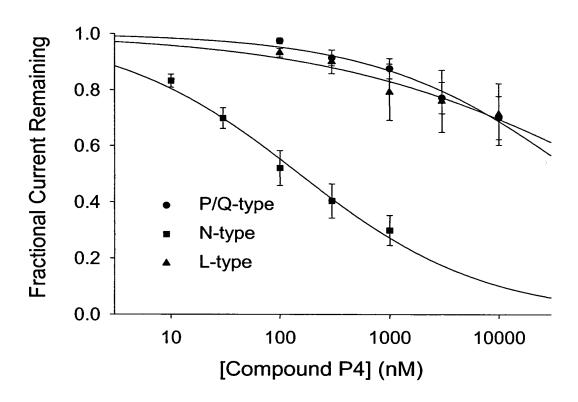
Inventor: Terrance P. SNUTCH et al.

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**BENZHYDRIL MOIETIES** 

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# Effect of Compound P4 on Various Ca<sup>2+</sup> Channels



$$IC_{50}$$
 P/Q-type >> 10  $\mu$ M (n=5)

$$IC_{50}$$
 N-type = 251 ± 103 nM (n=6)

$$IC_{50}$$
 L-type >> 10  $\mu$ M (n=5)

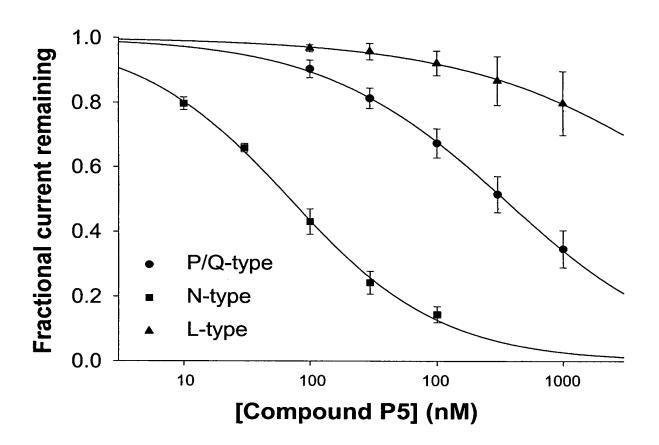
Figure 4

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## Selectivity of Compound P5 for N-type Ca<sup>2+</sup> Channels



P/Q-type IC<sub>50</sub> =  $5.028 \pm 1.979 \,\mu\text{M}$  (n=6) N-type IC<sub>50</sub> =  $0.073 \pm 0.01 \,\mu\text{M}$  (n=5) L-type IC<sub>50</sub> =  $210 \pm 130 \,\mu\text{M}$  (n=6)

Figure 5

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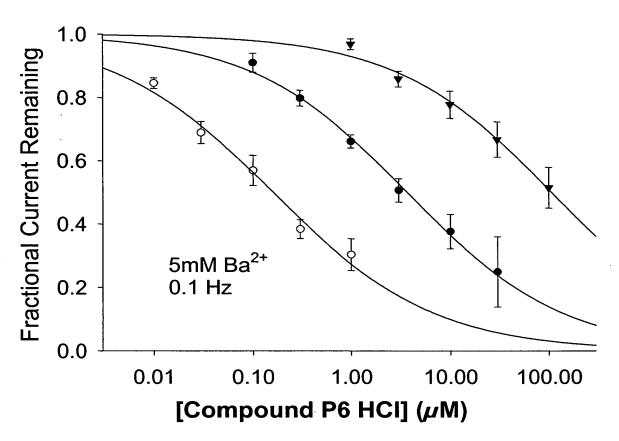
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**BENZHYDRIL MOIETIES** 

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# Selectivity of Compound P6 for N-type Ca2+ Channels



- P/Q-type IC<sub>50</sub> =  $4.5 \pm 1.3 \,\mu\text{M}$  (n=5)
- $\circ$  N-type IC<sub>50</sub> = 0.16 ± 0.03  $\mu$ M (n=5)

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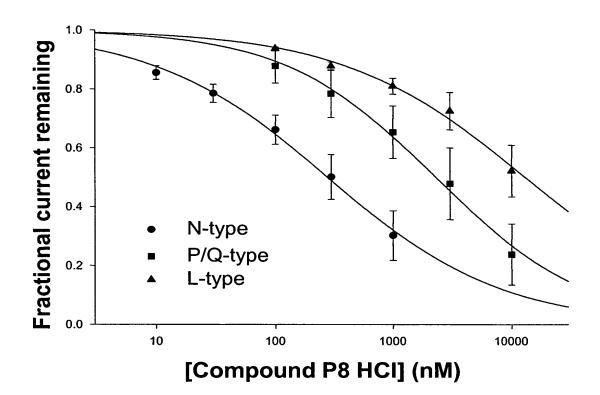
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### Selectivity of Compound P8 for N-type Ca2+ Channels



P/Q-type IC<sub>50</sub> =  $3.383 \pm 1.455 \,\mu$ M (n=5) N-type IC<sub>50</sub> =  $0.359 \pm 0.135 \,\mu$ M (n=5) L-type IC<sub>50</sub> =  $37.140 \pm 20.930 \,\mu$ M (n=5)